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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
FALK, ANNE MARIE

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/691,889	Applicant(s) FELD ET AL.	
	Examiner Anne Falk	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 April 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-37* is/are pending in the application.

4a) Of the above claim(s) *1-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *detailed action* .

DETAILED ACTION

The response filed April 23, 2002 (Paper No. 3) has been entered.

Claims 1-37 are pending in the instant application.

Applicants' election without traverse, of Group III, Claims 23-37, in Paper No. 3 is acknowledged. The elected invention is directed to a method of modifying the electrophysiological function of an excitable tissue region of an individual by transplanting cells, either genetically modified cells or unmodified cells.

Claims 1-22 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention. Applicant timely traversed the restriction requirement in Paper No. 3.

Accordingly, Claims 23-37 are examined herein.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

Claims 23-37 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification asserts that the present invention (*i.e.*, the method of cellular implantation) can be used for restoring normal electrophysiological function to damaged tissues such as heart, nerve, or glandular tissues (p. 9, lines 4-7). Thus, the claimed method encompasses treatment of a wide variety of disorders. The specification does not assert any use, other than treatment, for the claimed method of

cellular implantation. Claim 33 recites that the method is utilized for regulating cardiac arrhythmia. Claim 34 recites that the method is utilized for regulating secretion of endogenous factors from an organ including the excitable tissue region of the individual. Claim 35 recites that the method is utilized for regulating neuronal discharge.

The claims cover cell therapy, *in vivo* gene therapy, and *ex vivo* gene therapy. See, for example, Claim 25 which recites that the implanted cell is transformed, prior to, or following implantation, with an exogenous polynucleotide expressing at least one polypeptide capable of forming a functional ion channel or transporter. Claims 23, 24, and 28-35 cover the use of cells that are not genetically modified, as well as those that are genetically modified.

The teachings of the specification are limited to analysis of conduction properties of cells in cultures in a variety of assays (Examples 1-5, pages 33-57). The specification does not provide any working examples with regard to treatment of a diseased animal by implantation of cells as recited in the claims.

The nature of the invention relates to treatment of patients having a variety of deficits in excitable tissues. The claims are broad in scope, encompassing a wide variety of diseases and disorders, including epilepsy, diabetes, and cardiac arrhythmias.

The specification fails to provide an enabling disclosure for producing a therapeutic effect using the claimed method because methods of cellular transplantation and gene therapy are not routinely successful. The art teaches that therapeutic strategies that rely on methods of cellular transplantation and/or gene therapy are unpredictable.

Unpredictability in the Gene Therapy Art

The claimed invention is directed to methods of gene therapy. However, gene therapy is not routinely successful. Therefore, the disclosure must enable the full scope of the claimed methods and compositions with specific guidance. However, the specification fails to adequately teach a method for

using a cell as recited in the claims wherein the cell is transformed with an expression vector prior to, or following implantation, to produce a therapeutic effect. The specification does not provide specific guidance for the use of gene transfer vectors encoding an ion channel protein, transporter, or gap junction protein, particularly with regard to targeted gene delivery, the route and time course of administration, when, where, or for how long the gene should be expressed, the frequency of administration of the gene therapy vector, or in some embodiments, the intended target tissue, for improving function within an excitable tissue in an immunocompetent animal. The specification also lacks working examples showing that vectors comprising genes encoding ion channel proteins, transporter protein, and gap junction proteins could be used to deliver the gene to the appropriate site, and that once delivered the gene would be expressed at a level sufficient to provide adequate product to effect the desired therapy (i.e., improved function within the excitable tissue) in an immunocompetent animal. At the time the application was filed, the art of administering any type of genetic expression vector to an individual so as to provide a tangible therapeutic benefit was poorly developed and unpredictable. The NIH ad hoc committee to assess the current status and promise of gene therapy reported in December 1995 that "clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol, despite anecdotal claims...," and that "significant problems remain in all basic aspects of gene therapy" (Orkin and Motulsky, p. 1). In a review article published in Scientific American in June 1997, Theodore Friedmann discusses the technical barriers which have so far prevented successful gene therapy, and states "So far, however, no approach has definitively improved the health of a single one of the more than 2,000 patients who have enrolled in gene therapy trials worldwide" (p. 96). In a review article published in Nature in September 1997, Inder Verma states "Although more than 200 clinical trials are currently underway worldwide, with hundreds of patients enrolled, there is still no single outcome that we can point to as a success story" (p. 239). The instant specification does not adequately teach one skilled in the art how to practice the claimed methods nor does it teach how to use the claimed method to improve function in an

excitable tissue. Thus, absent any showing that polypeptide-encoding nucleic acids can be used to produce the intended therapeutic effect in an immunocompetent animal, such as a human, rat, mouse, etc., the claimed methods are not enabled by the disclosure. As gene therapy is not routine for the reasons discussed herein, undue experimentation would have been required for one skilled in the art to practice the claimed method, particularly over the full scope, which is very broad.

The specification fails to provide an enabling disclosure for targeting appropriate cells using vectors comprising polypeptide-encoding nucleic acids. Only general guidance is offered with regard to targeting strategies known in the art. However, the art recognizes that targeting strategies are not currently sufficient to overcome the problems known in the art. More importantly, the disclosure does not offer a solution to this problem, such that a wide variety of vector types, including both viral and non-viral vectors, could be used to improve function within an excitable tissue. While progress has been made in recent years for *in vivo* gene transfer, vector targeting to desired tissues *in vivo* continues to be unpredictable and inefficient as supported by numerous teachings in the art. For example, Miller et al. (1995) review the types of vectors available for *in vivo* gene therapy, and conclude that "for long-term success as well as the widespread applicability of human gene therapy, there will have to be advances ... targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (page 198, column 1). Deonarain et al. (1998) indicate that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain et al. review new techniques under experimentation in the art which show promise but states that such techniques are even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). Verma et al. (1997) review vectors known in the art for use in gene therapy and discuss problems associated with each type of vector. The teachings of Verma et al. indicate that a resolution to vector targeting has not been achieved in the art

(see entire article). Verma et al. also teach that appropriate regulatory elements may improve expression, but that it is unpredictable which tissues such regulatory elements target (page 240, sentence bridging columns 2 and 3). Crystal et al. (1995) also review various vectors known in the art and indicate that "among the design hurdles for all vectors are the need to increase the efficiency of gene transfer, to increase target specificity and to enable the transferred gene to be regulated" (page 409).

Even expression studies in animals are often not predictive that the same or similar results can be achieved in patients or that such expression would alleviate clinical symptoms. For example, although researchers have demonstrated expression of the CFTR gene in the surface airway cells of laboratory animals, problems transferring sufficient quantities of the CFTR gene into patients' cells have prevented the method from providing therapeutic benefit. Furthermore, the viral vector used to transfer the gene provoked an immune reaction in some patients (Marshall, 1995, p. 1052). Marshall emphasizes that the central challenge in the field of gene therapy is to find safe vectors capable of transporting genes efficiently into target cells, and getting the cells to express the genes once they are inserted. These problems remain unresolved.

The court has recognized that physiological activity is unpredictable. *In re Fisher*, 166 USPQ 18 (CCPA 1970). In cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved. *In re Fisher*, 166 USPQ 18 (CCPA 1970).

It is not to be left up to the skilled artisan to figure out how to make the necessary starting materials and then to figure out how to use them to produce the biological effects as recited in the claims. The courts held that the disclosure of an application shall inform those skilled in the art how to use applicant's claimed invention, not how to **find out** how to use it for themselves. *In re Gardner et al.* 166 USPQ 138 (CCPA 1970). This specification only teaches what is intended to be done and how it is intended to work, but does not actually teach how to do that which is intended.

In view of the quantity of experimentation necessary to determine appropriate parameters for practicing the claimed method to achieve improved function within excitable tissues in immunocompetent animals, and given the lack of applicable working examples directed to administering polypeptide-encoding nucleic acids to achieve improved function within excitable tissues, the limited guidance in the specification with regard to the design and implementation of vectors, the broad scope of the claims with regard to the type of vector to be used, the type of polypeptide-encoding nucleic acid to be used, and the wide variety of animal species to be treated, and the unpredictability in the gene therapy art, undue experimentation would have been required for one skilled in the art to practice the claimed method, particularly over the full scope.

Unpredictability in the Cell Transplantation Art

The specification fails to provide an enabling disclosure for the method of cell-based therapy because methods of transplantation of neural tissue or other cells into the animal body are not routinely successful and the specification does not offer adequate guidance to enable one skilled in the art to practice the claimed invention to derive a therapeutic benefit in a diseased animal. The specification teaches that the only use for the claimed method of transplantation is to produce a therapeutic effect, but the specification does not adequately teach how to use the claimed method to produce such an effect. Jackowski et al. (1995) details the limitations and unpredictability associated with the transplantation of neural tissue. At page 311, column 1, paragraph 2, the reference discusses barriers to successful transplantation of neural tissue, notably the presence of molecules that actively inhibit the regeneration of mammalian CNS and PNS axons. The specification does not offer any guidance as to how the claimed method could be used therapeutically for the treatment of any disorder, including epilepsy, diabetes, or cardiac arryhthmia. No working examples demonstrate a therapeutic effect for the claimed method of transplantation. The specification provides general teachings only, but does not provide specific guidance

for treating a pathological condition. The specification fails to provide any guidance relating to the number of cells to inject, the site of injection, and the extent of cellular persistence required and attainable in practice, to provide any therapeutic benefit for the treatment of any disorder.

The court has recognized that physiological activity is unpredictable. *In re Fisher*, 166 USPQ 18 (CCPA 1970). In cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved. *In re Fisher*, 166 USPQ 18 (CCPA 1970).

It is not to be left up to the skilled artisan to figure out how to make the necessary starting materials and then to figure out how to use them to produce the biological effects as recited in the claims. The courts held that the disclosure of an application shall inform those skilled in the art how to use applicant's claimed invention, not how to **find out** how to use it for themselves. *In re Gardner et al.* 166 USPQ 138 (CCPA 1970). This specification only teaches what is intended to be done and how it is intended to work, but does not actually teach how to do that which is intended.

In view of the limited guidance in the specification, the lack of applicable working examples, the unpredictability in the art of gene therapy and cellular transplantation as therapeutic strategies for the wide variety of disorders contemplated in the specification, the broad scope of the claims, and the lack of specific guidance regarding how to use the claimed method to produce a therapeutic effect in an individual, undue experimentation would have been required for one skilled in the art to practice the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 23-37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 23-37 are indefinite in their recitation of "[a] method of modifying the electrophysiological function of an excitable tissue region in an individual" because there is no conclusory statement indicating that the desired effect has been achieved. The method steps only recite implanting cells, but do not recite that said implantation produces modification of the electrophysiological function of the excitable tissue region into which the cells have been implanted. Thus, the steps are in conflict with the preamble.

Claims 23-37 are indefinite in their recitation of "capable of" because a capability is only a potential property and not an actual property. The term "capable of" implies conditionality, but the claims do not recite the conditions under which the potential property becomes an actual property. Thus, there is no requirement that gap junctions actually form or that ion channels actually form upon implantation of the cells.

Claim 37 is indefinite in its recitation of "functional pap junctions" because "pap" appears to be a typographical error for "gap."

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Falk whose telephone number is (703) 306-9155. The examiner can normally be reached Monday through Thursday and alternate Fridays from 10:00 AM to 7:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

Anne-Marie Falk, Ph.D.

Anne-Marie Falk

ANNE-MARIE BAKER
PATENT EXAMINER